



# **Armed Forces College of Medicine AFCM**



# **Myasthenia Gravis**

**Recorded by**

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# INTENDED LEARNING OBJECTIVES (ILO)



**By the end of this lecture the student will be able to:**

**1- Classify the drugs used in treatment of myasthenia gravis**

**2- Explain the mechanism of action and adverse effects of drugs used in treatment of myasthenia gravis**

# Introduction



- **Myasthenia gravis (MG)** is an autoimmune disorder affecting neuromuscular transmission, Leading to generalized or localized muscle weakness characterized by easy fatigability, Severe disease may affect all the muscles, including those necessary for respiration.
- **It is due to production of auto-antibodies against acetylcholine receptors** (antibodies against Motor End Plate (M.E.P.)). In this disease, antibodies are produced against the main immunogenic region found on  $\alpha 1$  subunits of the nicotinic receptor channel complex. **Antibodies are**

# Introduction

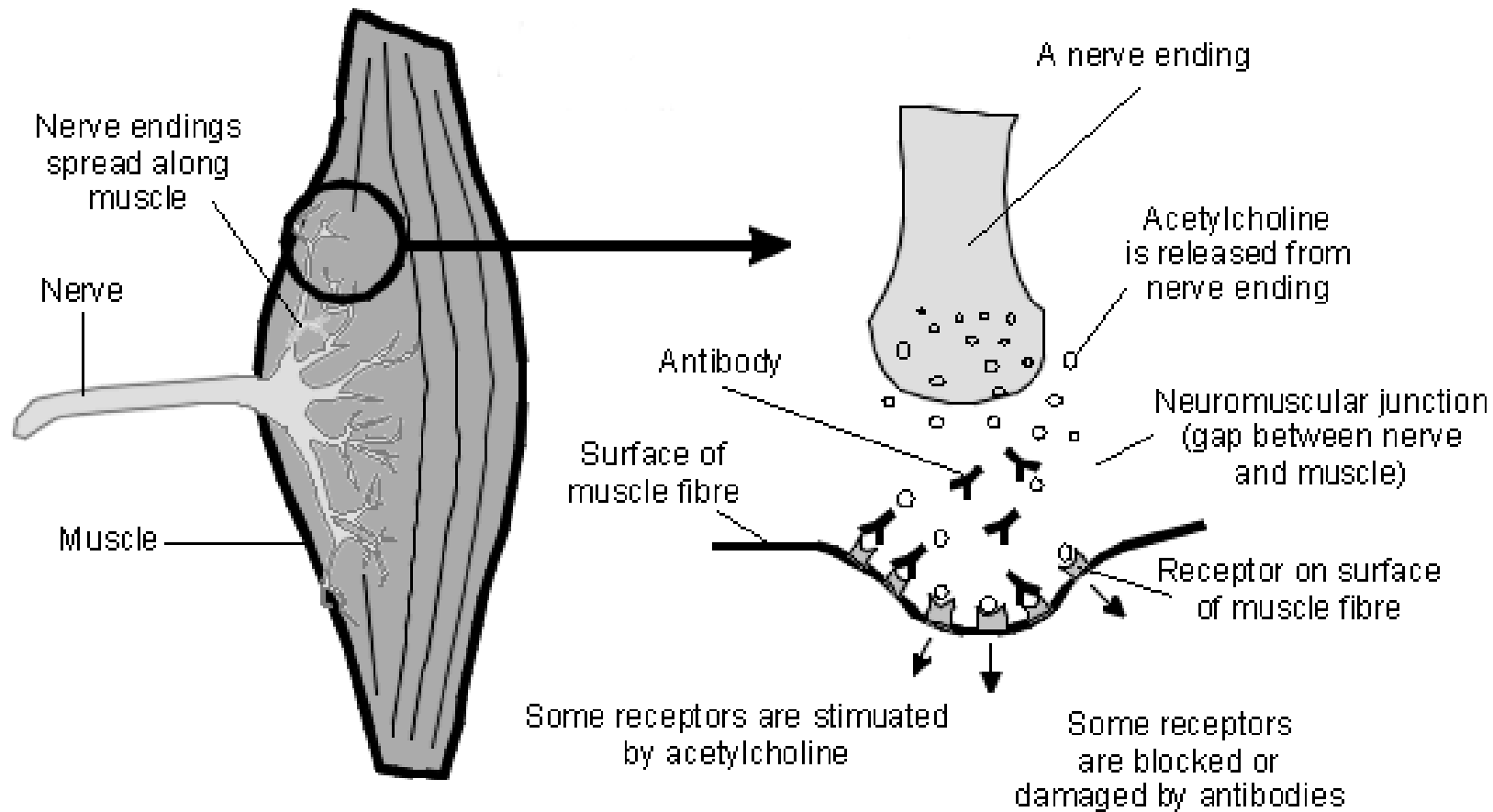


## The antibodies reduce nicotinic receptor function by:

- (1) Cross-linking receptors, a process that stimulates their internalization and degradation
- (2) Causing lysis of the postsynaptic membrane
- (3) Binding to the nicotinic receptor and inhibiting function.

Frequent findings are ptosis, diplopia, difficulty in speaking and swallowing, and extremity weakness

# Introduction

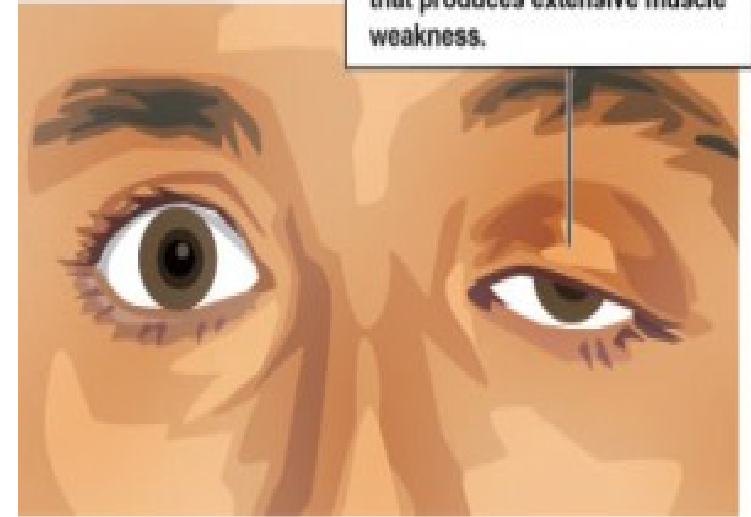


# Clinical Picture



- Fatigue with muscle use
- Double vision, droopy eyelids, trouble swallowing/chewing
- Facial weakness
- Shortness of breath
- **Myasthenic crisis** is a complication of myasthenia gravis characterized by worsening of muscle weakness, resulting in respiratory failure that requires intubation and mechanical ventilation

A drooping eyelid, is the most frequent early sign of myasthenia gravis, a disease that produces extensive muscle weakness.



# Cholinergic and Myasthenic crisis



Cholinergic crisis	Myasthenic crisis
<b>Due to:</b> <b>Excessive ChE inhibition (over dose) → Maintained depolarization at N-M junction.</b>	<b>Due to:</b> <b>Insufficient treatment with: Choline esterase inhibitors.</b>
<b>I.V Edrophonium</b> <b>→ produces more weakness.</b>	<b>I.V Edrophonium</b> <b>→ produces muscle improvement.</b>



# To differentiate between cholinergic and myasthenic crisis:

**Edrophonium IV** is used.

- It is a **Reversible** choline esterase inhibitor.
- Shortly** acting (duration 5 min).

**Also**, Edrophonium can be used as a pharmacological test in **diagnosis** of myasthenia gravis → improvement of symptoms (**Edrophonium IV + Atropine**).

# Treatment of Myasthenia Gravis



## 1- Anticholine esterase:

❖ **Neostigmine** : is a reversible cholinesterase inhibitor □ inhibits the degradation of Acetylcholine(Ach) □ Accumulation of Ach.

↑ Acetylcholine concentration □ stimulate both Nicotinic (Nm in N-M junction) & Muscarinic receptors.

↑ **skeletal muscle power, used orally in treatment of myasthenia gravis.**

# Neostigmine Substitutes



- ❖ **Pyridostigmine**
- ❖ **Ambenonium**

## Reversible cholinesterase inhibitor

Preferred to neostigmine in myasthenia gravis :

- More specific.
- Longer duration of action.
- Fewer visceral side effects.
- ↑ selectivity on skeletal muscles compared to it.

# Neostigmine Substitutes



Edrophonium		Pyridostigmine & Ambenonium
<b>Selectivity:</b>	<b>Skeletal muscle</b>	<b>Skeletal muscle</b>
<b>Duration:</b> <b>5 min</b>	<b>Short</b>	<b>Longer duration</b>
<b>Uses:</b> <ul style="list-style-type: none"> <li>1- Diagnosis of M.gravis</li> <li>2- ttt of myasthenic crisis due to under ttt (improve patient)</li> <li>3- Diagnosis of cholinergic crisis due to over ttt</li> </ul>		ttt of myasthenia gravis (more specific - longer duration)

# Treatment of Myasthenia Gravis



## 2- Atropine:

Atropine causes reversible competitive blockade of the actions of Ach at muscarinic receptors (**non-selective muscarinic receptors blocker**).

Atropine is added to block the unwanted side effects of reversible anticholine esterase which result from stimulation of muscarinic receptors by the accumulated Acetylcholine.

# These unwanted side effects are:

## - **Muscarinic:**

Bradycardia, hypotension, bronchospasm, miosis, vomiting, diarrhea, increase secretions (sweating, salivation, bronchial and lacrimation).

## - **Nicotinic:**

Sk. Muscle twitches, eye lid, facial, trunk.

# Treatment of Myasthenia Gravis

## 3- Adjuvant ttt:

**a- Ephedrine:** Potentiates Neostigmine  
(VD of skeletal BV + facilitate NM transmission)

**b- Caffeine:** Potentiates Neostigmine  
(Direct stimulation of ms)

## 4- Others:

**a- Immunosuppressants as corticosteroides :** Decrease antibody formation.

**b- Plasmapheresis** to wash acetylcholine receptor antibodies from the circulation.

**c- Thymectomy.**



# Immunomodulating therapy



## Corticosteroids

- Corticosteroids can suppress the immune system in several ways.
  - Prednisone has been shown to reduce acetylcholine receptor antibody levels

## Azathioprine

- Azathioprine (Imuran) is an antimetabolite that blocks T lymphocytes proliferation.
- Azathioprine is used most often in patients who have relapsed while on prednisone or as a steroid-sparing agent in patients who have been taking prednisone for long periods of time

# Immunomodulating therapy



## Cyclosporine

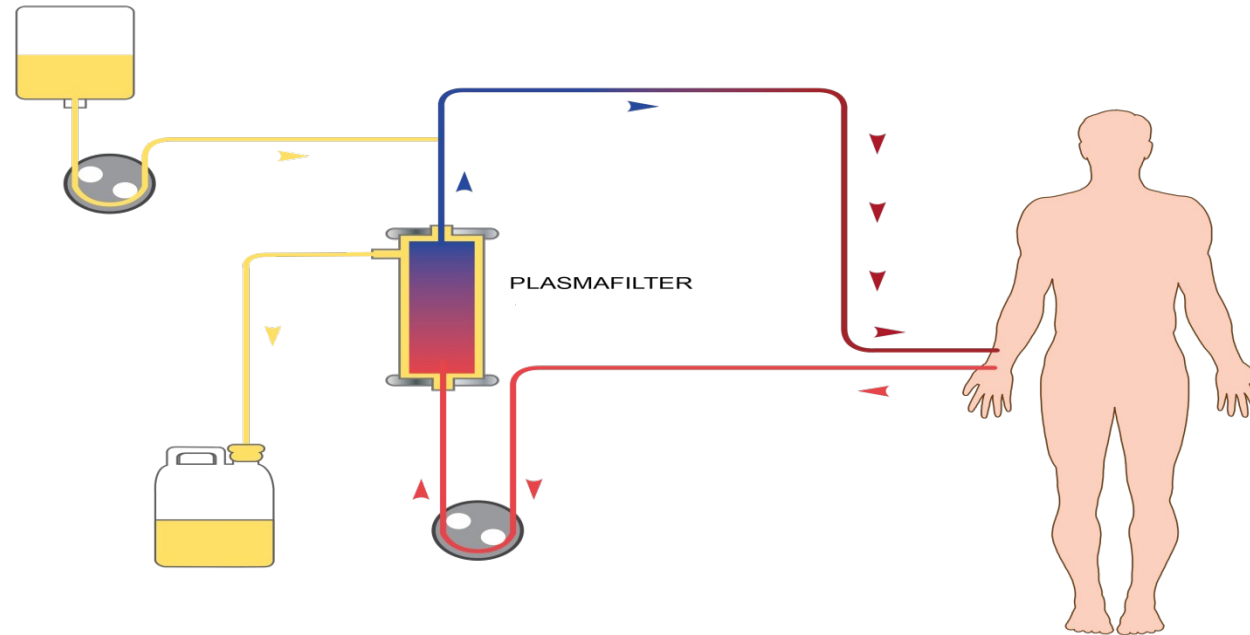
- Cyclosporine (Sandimmune, Neoral), a drug designed to prevent rejection in organ transplantation patients
- Inhibits T cell proliferation by inhibiting IL-2 secretion.

## Mycophenolate Mofetil

- MyM (CellCept) is another immunosuppressive agent used in organ transplantation.
- By selectively blocking purine synthesis it suppresses both T- and B-cell proliferation.

## Intravenous Immunoglobulin

# Plasmapheresis



- Plasmapheresis, a procedure that removes acetylcholine receptor antibodies from the circulation.
- **Improvement following plasmapheresis occurs within a few days, much faster than for other immunomodulating therapies.**
- Plasmapheresis is an established therapy for patients in myasthenic crisis

# Drugs contraindicated in Myasthenia Gravis



- 1-Skeletal muscle relaxants**
- 2-Aminoglycosides**
- 3-Lithium**
- 4-Beta blockers e.g. propranolol**
- 5-Anti-arrhythmics e.g. quinidine & lidocaine**

# Summary of Myasthenia Gravis



Autoimmune disease characterized by muscle weakness & easy muscle fatigability due to formation of antibodies against Motor End Plate (M.E.P.)

## Diagnosis:

Edrophonium IV + Atropine

## Treatment:

**1- Antich. esterase:** Neostigmine or pyridostigmine

**2- Atropine:** block unwanted muscarinic actions.

**3- Adjuvant ttt:** a- Ephedrine: b- Caffeine

**4- Others:** a- Cortisol      b- Plasmapheresis      c-

# Lecture Quiz



**1)- The following drug is contraindicated in myasthenic patients:**

- a- Aminoglycoside
- b- Ephedrine
- c- Caffeine
- d- Cortisol

**a- Aminoglycoside**

# Lecture Quiz



**2)- The following drug is used in the diagnosis of myasthenic patients:**

- a- Pyridostigmine
- b- Ambenonium
- c- Edrophonium
- d- Lithium

**c- Edrophonium**

# Lecture Quiz



**3)- All of the following drugs are used in the treatment of myasthenic patients EXCEPT:**

- a- Pyridostigmine
- b- Neostigmine
- c- Atropine
- d- Curare

**d- Curare**



# SUGGESTED TEXTBOOKS



1- Whalen, K., Finkel, R., & Panavelil, T. A. (2018) Lippincott's Illustrated Reviews: Pharmacology (7th edition.). Philadelphia: Wolters Kluwer

2- Katzung BG, Trevor AJ. (2018). Basic & Clinical Pharmacology (14th edition) New York: McGraw-Hill Medical.

# THANK YOU

